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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/347,064 | 07/02/99 | ECK J | 09282-5(B352 |

000570 HM22/1022
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| EXAMINER | |
|---|---|
| JAMROZ,M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | 17 |

**DATE MAILED:** 10/22/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Offic Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/347,064 | ECK ET AL. | |
| | Examiner | Art Unit | |
| | Margaret E Jamroz | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27,29 and 32-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-27, 29, and 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *notide to comply* .

| Notice to Comply | Applicati n N . | Applicant(s) | |
|---|---|---|---|
| | 09/347,064 | ECK ET AL. | |
| | Examiner | Art Unit | |
| | Margaret E Jamroz | 1644 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1 825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: A sequence recited in claim 8 has not been given in the proper form as a SEQ ID NO.

### Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

**PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY**

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating papers for this application, all further correspondence regarding this application should be directed to Megan Jamroz in Art Unit 1644, Technology center 1600.

2. The request filed on July 27, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/347,064 is acceptable and a CPA has been established. An action on the CPA follows.

3. Applicant's amendment, filed on July 27, 2001 (Paper No. 8), is acknowledged.

Claims 28, 30, 31, and 38-46 have been canceled previously.

Claims 8, 15, 16, and 26 and have been amended.

Claims 1-27, 29, and 32-37, are pending and being acted upon presently.

4. Applicant's election without traverse of Group I, claims 1-27, 29, and 32-37, and the species:

A) Effector module: SEQ ID NO:1,

B) Processing module: SEQ ID NO:5,

C) Targeting module: basic fibroblast growth factor (bFGF),

D) Modulating module: SEQ ID NO:3,

E) Affinity module: SEQ ID NO 17,

in Paper No.8, is acknowledged.

Note that claim 32 is being examined only as it pertains to a nucleic acid.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim 8 recites "(ii) the sequence S4-S3-S2-S1/S1'" which is a sequence and should be disclosed as a SEQ ID NO.

Applicant is reminded to amend the specification (including the Brief Description of Drawings) and claims as appropriate to reflect compliance with the Sequence Rules.

6. The instant claims have the benefit under 35 U.S.C. 120 of the parent filing date. The subject matter claimed in Claims 1-27, 29, and 32-37 are supported in the parent application Serial Number 09/347,064 and following. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the parent application.

7. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Applicant's provision of a translation of the foreign priority document is acknowledged, filed on July 27, 2001 (Paper No: 8).

8. In contrast to priority under 35 U.S.C. 120, the instant claims do not appear to have written support to the foreign priority document EP97 10 0012.0 (02 Jan 1997) as evidenced by the translation, filed on July 27, 2001 (Paper NO: 14).

Claim 1 recites a nucleic acid molecule that has "at least a fragment of" a SEQ ID NOS: 1, 2, 5, and 6. The phrase "at least a fragment of" broadens the scope of the claim.

Claims 2-33 depend on claim 1.

Claims 2-3 recites an effector molecule which "has at least one" amino acid deletion, etc. The phrase "at least one" broadens the scope of the claim.

Claim 5 recites a molecule which "encodes at least a fragment" and "of at least a fragment" SEQ ID NOS: 3 and 4. The phrase "at least" broadens the scope of the claim beyond the priority document.

Claim 6 depends on claim 5, which depends on claim 1. Additionally, it recites a nucleic acid molecule which "has at least one". The phrase "at least one" broadens the scope of the claim.

Claims 17 recites amino acid exchanges at positions "68, 70, 75, and 249" which lack antecedent basis in the instant specification. The additional residues available for modification change the scope of the claim.

Claim 18 recites "substitution of S at position Y68, substitution of S at position Y70, substitution of S at position Y75, and substitution of S at position F79" which lack antecedent basis in the instant specification. The additional residues available for modification change the scope of the claim.

Claim 32, recites a medicament comprising (a) one of (i) **and** (ii); and (b) one of (iii) **and** (iv). The translated priority document recites a medicament comprising (a) one of (i) **or** (ii); and (b) one of (iii) **or** (iv). The change from and to or changes the scope of the claim.

Claim 34 recites a molecule "encoding at least a fragment" and "a sequence of at least a fragment" of SEQ ID NOS: 1 and 2. The phrase "at a fragment of" broadens the scope of the claim.

Claim 35 depends on claim 34.

Claim 36 recites a molecule "encoding at least a fragment" and "a sequence of at least a fragment" of SEQ ID NOS: 5 and 6. The phrase "at a fragment of" broadens the scope of the claim.

Claim 37 depends on claim 36.

9. Applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112, first paragraph.

***Abstract***

10. The abstract of the disclosure is objected to because the maximum length of an abstract is 150 words.

Correction is required. See MPEP § 608.01(b).

***Claim R j ctions - 35 USC § 112***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

12. Claims 1-27, 29, and 32-37 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. Upon reconsideration of the amendment and new Sequence Listing, filed 2/28/00 (Paper No. 8), the following is noted.

The amendment, including the Sequence Submission filed 2/28/00 (Paper No. 8) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The paper copy of the sequence listing with respect to SEQ ID NOS: 5 and 6. Applicant's amendment simply asserts that upon reviewing the paper copy of the sequence listing, applicant has noted that the sequence listing filed with the application included correct sequences for SEQ ID NOS: 5 and 6 and a corrected sequence has been filed.

Applicant is required to submit a declaration by a person in a position to corroborate the fact which attests that the changes made to the nucleic acid (and/or amino acid) sequence(s) shown in Figures 5 and 6 were made to correct errors occurring in the original sequence(s) and that the corrected sequences were obtained by sequencing the identical source material as identified in the originally filed specification. The declaration should be accompanied by evidence documenting that the changes made, correct errors discovered in the original sequence data. Also, see MPEP 2422.08.

Even if there is a discrepancy between the computer readable form and the Sequence listing, applicant is required to submit a declaration by a person in a position to corroborate the fact which attests that the changes made in the amendment, filed on 2/28/00 (Paper No. 8) were consistent with the biological materials disclosed in the specification as filed.

14. Claims 1-27, 29, and 32-37 all recite a targeting molecule that is (SEQ ID NOS: 5 and 6). All claims are rejected as they depend on new matter.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.
Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.

Given the new matter issues above, the instant application does not appear to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

15. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the *Wands* factors (MPEP 2164.01 (a)).

*Nature of the invention.* The claims are drawn to a "medicament" for use in methods of treatment of a patient with a polynucleotide. The method comprises transporting a polynucleotide across a biological barrier to a cell, wherein the polynucleotide must be translated into protein and the protein then processed and cleaved by the cell.

*Breadth of claims.* The claims are broad, encompassing delivery of a polynucleotide for treatment of a subject. A specific treatment is not defined in the claim nor the specification, however, a general discussion on the use of the composition for the delivery of a polynucleotide and its potential usefulness for 'gene therapy' is discussed.

*State of the prior art.* At the time of the invention was made, successful use of "a medicament comprising a nucleic acid" had not been demonstrated. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Anderson W.F. (Nature, 1998. 392(Supplement): 25-30) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, column 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30).

*Working Examples and Guidance in the specification.* There are no working examples nor guidance regarding the method of treatment.

*Predictability of the art.* The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). Since the applicants have not described all the nucleic acids encompassed by the claims, there is no way to predict efficiency of delivery to nor expression of the polynucleotide in the desired target cell. Further, the specification does not disclose all claimed specific target cells.

*Amount of experimentation necessary.* Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, W.F. Nature, 1998. 392(Supplement): 25-30, and especially page 30; of record), it would require extensive research to understand the fundamental biology of the system. Applicants have described a composition for the delivery of a polynucleotide for gene therapy, but essentially all of the work required to ultimately develop therapeutic methods has been left for others.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill in the art at the time the invention was made to practice the invention as claimed.

16. Claims 1-27, 29, and 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a fusion protein consisting of:

A) an effector module consisting of SEQ ID NO:1,
B) a processing module consisting of SEQ ID NO:5,
C) a targeting module consisting of bFGF,
D) a modulating module consisting of SEQ ID NO:3,
E) an affinity module consisting of SEQ ID NO 17,

does not reasonably provide enablement for nucleic acids encoding fusion protein "fragments" and "derivatives" thereof, as well as nucleic acid molecules which "hybridize" or are "degenerate", or nucleic acids (e.g. Claim 1, (iii), (iv)) encoding fusion proteins containing amino acid deletions, substitutions, insertions, additions, or exchanges (e.g. Claim 3) as it reads on the elected invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed in claims 1-27, 29, and 32-37 without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of protein/peptide encoding nucleic acids broadly encompassed by the claims.

The terms "fragment" and "derivative" (claims 1, 16, 34, 36, and 37), and "deletion, "substitution", "insertion", "addition", or "exchange" (claims 2, 3, 4, and 6) "hybridize" (claims 1, 5, 34, and 36), and "degenerate" (claims 1, 5, 34, and 36), are open-ended and include all homologues, fragments, degenerates, nucleic acids which hybridize, and synthetic variants of the recited amino acid sequences. The specification fails to provide sufficient guidance regarding the specific properties required to determine whether a polypeptide or a fragment thereof encoded by the claimed nucleic acid is a functional effector, processing, modulating, targeting, or affinity module.

It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, the Mikayama et al. (of record) reference teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. (Proc. Natl. Acad. Sci., 1993. 90:10056-60) teaches further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Additionally, Skolnick and Fetrow (Trends in Biotechnology, 2000. 18(1):34-9) teach that determining the sequence of a nucleic acid molecule does not provide sufficient information to obtain the structure of a protein. Furthermore, the function of a protein cannot be determined simply by knowing the structure of a protein, as many proteins are multifunctional. Changes in nucleic acid sequences can, therefore, potentially result in changes in essential three-dimensional structures of the given protein, and consequently, it's function.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of proteins. Therefore, structurally unrelated nucleic acids having or encoding "at least a fragment" encompassed by the claimed invention other than "nucleic acids set forth by SEQ ID NOS: 1-6 and 17" would be expected to have greater differences in their activities. For example, it is noted that lectins and growth factors do not share critical common structural attributes, as lectins and growth factors differ in structure and physicochemical properties.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which fragments will retain functionality requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure and therefore function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to functional effector, processing, targeting, modulating, and affinity modules with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

Additionally, the specification discloses that efficient intracellular protease cleavage requires the un-glycosylated protein as is produced in bacterial vectors, thus claims 25-26 drawn to nucleic acids in glycosylating eukaryotic hosts are not enabled. The processing molecules will be examined as proteases, as proteases are the only processing module with sufficient support in the instant specification as disclosed on page 13, paragraph 1.

In re Fisher, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

17. Claims 1-27, 29, and 32-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein

There is insufficient written description to show that, other than a nucleic acid encoding a fusion protein consisting of:

A) an effector module consisting of SEQ ID NO:1,
B) a processing module consisting of SEQ ID NO:5,
C) a targeting module consisting of bFGF,
D) a modulating module consisting of SEQ ID NO:3,
E) an affinity module consisting of SEQ ID NO 17,

Applicant was in possession of a nucleic acid encoding a fusion protein comprising:

A) a "fragment" or "derivative" of the mistletoe lectin A chain (claims 1 and 37).
B) a "fragment" or "derivative" of the mistletoe lectin B chain (claim 16).
C) a "fragment" or "derivative" of the mistletoe lectin propeptide (claims 1 and 36).

The specification defines "hybridize" only for nucleic acid molecules which bind to SEQ ID NOS 1-6,and "degenerate" only for those molecules which "hybridize". The specification fails to define "hybridize" and "degenerate". The lack of sufficient limitations would therefore allow for *any* number of *any* substitutions, insertions, deletions, exchanges, and/or additions and thus define *any* nucleic acid. Further, the specification provides insufficient guidance as to how to identify nucleic acids which "hybridize" and are "degenerate", other than trial and error in an *in vitro* assay. Therefore, the skilled artisan cannot envision all the contemplated nucleic acid and amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The specification defines "fragment" only for the mistletoe A chain and then only as a peptide "which exhibits intracellular toxic activity". The specification fails to define "derivative". The lack of sufficient limitations would therefore allow for *any* number of *any* substitutions, insertions, deletions, exchanges, and/or additions and thus define *any* nucleic acid encoding *any* protein. Further, the specification provides insufficient guidance as to how to identify intracellularly toxic peptides, other than trial and error in a killing assay. One of skill in the art would therefore conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See Eli Lilly, 119 F.3d 1559, 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Alternatively, Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

18. For examination purposes, the recitation of "has" or "having" is being interpreted as being "open" (i.e. "comprising"). Therefore, the recitation of "has" or "having" opens the claims up to include un-recited elements even in large amounts. Applicant is invited to amend the claims to recite "comprising" or "consisting of" for clarity.

19. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP 608.01(o). Correction of the following is required:

Claim 8 recites "[and] neither S3 nor s4 is proline, and S1' is any amino acid residue", which are not disclosed in the instant specification on pages 22-23, paragraph spanning the end of page 22 and beginning of page 23.

Claim 17 recites "amino acid changes at positions 68, 70, 75, 79, and 249", which are not disclosed in the instant specification on page 15, lines 20-24.

20. Claims 35 and 37 are objected to under 37 CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claims.

## *Claim Rejections - 35 USC § 112*

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

22. Claims 1-27, 29, and 32-27 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-27, 29, and 34-37 are indefinite in the recitation of "a nucleic molecule which hybridizes" and is "degenerate" because the metes and bounds of such conditions are ambiguous and unclear and, in turn, the metes and bounds of the claimed "nucleic acid molecules" are not defined.

B. Claims 1, 5, 8, 10-11, 13-14, 16, 34, and 36 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record set forth on Paper No. 9, mailed 5/24/00.

Applicant's arguments, filed 11/27/00, have been fully considered but have not been found convincing. Applicant argues that "degenerate", "a cell of the specific immune system", "a cell of the unspecific immune system", "a degenerate cell of the immune system", "/" and the moiety "S1'", while undefined in the specification, would be understood by the skilled artisan. While the terms may have vaguely defined meanings within the art, said terms are still ambiguous and render the claims indefinite.

Applicant's arguments have been acknowledged, but there is insufficient objective evidence and written description to support applicant's position. Applicant's arguments are not found persuasive.

C. The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

## *Claim Rejections - 35 USC § 103*

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 1-16, 19-27, 29, and 32-37 rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al (U.S. Patent No. 4,894,443), in view of Lappi et al (The Journal of Biological Chemistry, 1994. 269(17): 12552-12558), Wu et al. (Gene, 1997. 190(1): 157-162), and Dietrich et al (Anti-Cancer Drugs, 1992. 3:507-511) or Gabius et al. (Anticancer Research, 1992. 12: 669-675).

Greenfield et al. teach the preparation of recombinant conjugate toxins, including mistletoe comprising an enzymatically-active domain (encompassing an effector module), an intracellular cleavage site that provides a cleavage site (encompassing a processing module), a translocation or internalization facilitating domain (encompassing a modulating module), a polypeptide spacer, and a target cell binding moiety (a targeting module), thereby teaching nucleic acids (e.g. DNA and RNA), vectors, host cells, fusion proteins, and methods of making fusion proteins. (See the entire document) The main objective of the invention was to provide a novel toxin conjugate comprising a cytotoxic component, a polypeptide spacer encompassing a processing module, and a target cell-binding moiety. The non-binding portion of the molecule was constructed to retain it's cytotoxicity, intracellularly cleavable/extracellular stability, and translocation properties of the natural molecule in a manner that permitted the connection of the binding moiety and retaining activity. The synthetic fusion protein conjugate was constructed through a series of DNA manipulations in vectors, which were then transformed into E. coli for screening purposes. The toxins are useful in that they are potent cytocides in that they disrupt critical cellular functions. The invention also encompasses biochemistry, genetic engineering, and medicine (i.e. cancer treatment). (See entire document, including Figures and column 18, paragraph 4; column 3, paragraph 1; column 2, paragraph 2, column 1, paragraph 2)

Greenfield et al. did not teach the use of basic fibroblast growth factor as a targeting module, the vector pT7, the affinity module, or the claimed mistletoe lectin DNA or cDNA sequences per se.

Lappi et al. teach the use of the plasmid pT7 for purposes of cloning and expression of fusion proteins and the use of basic fibroblast growth factor within the context of a fusion protein encompassing a targeting module. Lappi et al. teach that the fusion protein was cytotoxically active in mouse melanoma cells, inhibited tumor growth, and exhibited antimetastatic activity in *in vivo* models of melanoma. Additionally, the fusion protein could target cytotoxic agents *in vivo*. (see entire document, including page 12553, column 2, paragraph 4)

Dietrich et al. teach the N-terminal sequences of several mistletoe lectin A chains which are 100% identity to the N-terminal sequence of MLA in the instant application (encompassing a fragment of mistletoe lectin A). Dietrich et al. specifically teach that Mistletoe lectin I increases the production of cytokines and has been proposed as a useful biological response modifies in the treatment of cancer. Mistletoe lectins II and III are also taught in this reference. All three toxins are recited as inhibiting the growth of a human tumor cell line (see entire document, including the abstract and Figure 3).

Gabius et al. also teach the N-terminal sequences of both mistletoe lectin A and B chains which are 100% identity to the N-terminal sequences of MLA and MLB in the instant application (encompassing a fragments of mistletoe lectins A and B) including the limitation of "S4-S3-S2-S1/S1'" encompassed by claims 1-27, 29, and 32-27. Pure, well-characterized lectins are an indispensable prerequisite as immunomodulators in clinical applications. Lectins have successfully suppressed clinical signs of experimental autoimmune myasthenia gravis as well as encephalomyelitis by preventing the induction of effector T cells by enhancing sensitization of cells in the suppressor pathway, partly by augmenting cytokine release (see entire document, including Figure 2 and the discussion).

Wu et al. teach the use of an in-frame 6 x His tag (encompasses an affinity module) in the nucleic acid sequence encoding a recombinant gfp cDNA fusion protein that allows for purification of the fusion protein on an agarose matrix after expression in bacteria. (See entire document, including the abstract, and Figure 2B)

Given the teachings of the prior art, including recombinant methods, vectors, host cells, and nucleic acids; one of ordinary skill in the art would have employed art known host cells (e.g. prokaryotic and eukaryotic) as set forth in claims 24-25 to produce fusion proteins of interest.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of the four secondary references to those of Greenfield et al. reference

Given the teachings of Greenfield to apply mistletoe in immunotoxins, one of ordinary skill in the art at the time the invention was made would have motivated to substitute the nucleic acids encoding mistletoe lectins A and B as taught by Dietrich et al. and Gabius et al. Both references teach that mistletoe lectins increase the production of cytokines, modify biological responses in the treatment of cancer, inhibit the growth of a human tumor cell line, act as immunomodulators in clinical applications, successfully suppress clinical signs of experimental autoimmune myasthenia gravis as well as encephalomyelitis by preventing the induction of effector T cells by enhancing sensitization of cells in the suppressor pathway.

Given the teachings of the prior art encompassing the use of immunotoxic fusion proteins (i.e. mistletoe) to treat tumors, increase the production of cytokines, modify biological responses in the treatment of cancer, inhibit the growth of a human tumor cell line, act as immunomodulators in clinical applications, successfully suppress clinical signs of experimental autoimmune myasthenia gravis as well as encephalomyelitis by preventing the induction of effector T cells by enhancing sensitization of cells in the suppressor pathway, one of ordinary skill in the art would have been motivated to make fusion proteins to target various cells, including the cells set forth in claims 9-14, depending on the nature of the targeted disease or condition.

Given the teachings of Lappi et al. to use FGF as a targeting molecule to treat tumors; one of ordinary skill in the art would have been motivated to substitute the FGF targeting moiety into the immunotoxins comprising mistletoe, as taught by to apply Greenfield et al.

One of ordinary skill in the art would have a reasonable expectation of success in using alternative or equivalent targeting moieties and effector moieties (i.e. recombinant fusion proteins) as taught by Lappi et al. who used a fusion protein encompassing an immunotoxin to successfully inhibit turmors and to exhibit anti-metastatic activity *in vivo* using the recombinant fusion protein.

One of ordinary skill in the art at the time the invention was made would have motivated to substitute the nucleic acids encoding mistletoe lectin A as taught by Greenfield et al. who specifically teaches the use of plant toxins, such as mistletoe, as a recombinant toxin conjugates.

Note that the claims are drawn to compositions comprised of a nucleic acid and that claimed recitation of intended use as a medicament or the recitation of a kit does not carry any patentable weight per se. While the claim recites a medicament or a kit, no positive recitation of the ingredients distinguishes it over the references; therefore the medicament or kit is encompassed by the references. However, if this is not the case, it is a well-known convention in the art to place these components in a kit for convenience and economy.

> In the absence of any recitation in the claims or any direction in the specification to the contrary, the recitation of a medicament or a kit reads on component parts capable of being assembled or a plurality of elements grouped together as a kit.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Allowable matter***

25. No claim is allowed.

***Conclusion***

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Megan Jamroz whose telephone number is (703) 308-8365. The examiner can normally be reached Monday through Friday from 8:00 AM to 4:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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